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(19)

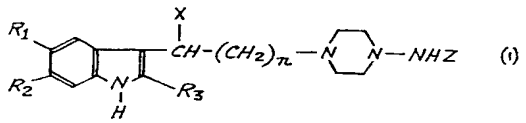
(54) 3-(4-AMINO- AND 4-ACYLAMINO-PIPERAZIN-1-YLALKYL) INDOLES

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt/Main 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 3-indoalkyl-amines and derivatives thereof.

3-Indoalkyl-amines are known and have been shown to possess important biological activity. Benzamidopiperidyl-ethylindoles are reported to be potent antihypertensive agents [Archibald et al., J. Med. Chem., *14*, 1054 (1971)], and 1 - [(3-indole)alkyl] - 4 - arylpiperazines are reported to be active as central nervous system depressants [Wylie et al., J. Med. Phar. Chem., *5*, 932 (1962)].

The present invention provides a compound of the general formula:



(I)

wherein

X represents a hydrogen atom or hydroxy group,

n represents 0 or 1,

R_1 and R_2, which may be the same or different, each represents a hydrogen atom or an alkoxy group having 1 or 2 carbon atoms, preferably methoxy,

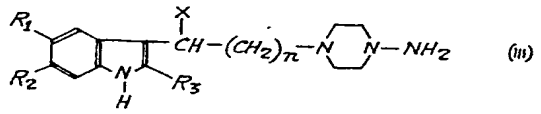
R_3 represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, preferably methyl, and

Z represents a hydrogen atom or a group of the formula —CO—R_4 wherein R_4 represents an alkyl group having from 1 to 4 carbon atoms, a benzhydryl group, a cycloalkyl group having from 6 to 10 carbon atoms, a bridged cycloalkyl group having from 6 to 10 carbon atoms, an unsubstituted or substituted phenyl group or an unsubstituted or substituted heterocyclic group, for example, a pyridyl, pyrrolyl, thienyl, pyrazinyl or, preferably, furyl group.

The present invention also provides a salt, especially a physiologically tolerable salt, of such a compound.

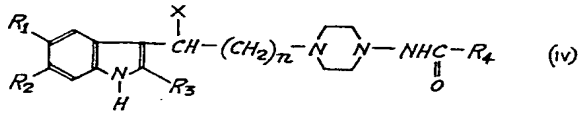
The compounds of formula I and their physiologically tolerable salts possess antihypertensive and tranquilising properties.

The compounds may be represented by the formula



(III)

wherein X, n, R_1, R_2 and R_3 have the meanings given above, and



(IV)

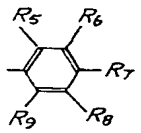
wherein X, n, R_1, R_2, R_3 and R_4 have the meanings given above, wherein preferably R_4 represents an alkyl group having 1 to 4 carbon atoms, a benzhydryl group, a cycloalkyl group having 6 to 10 carbon atoms, a bridged cycloalkyl group having 6 to 10 carbon atoms with the bridging member having from 1 to 3 carbon atoms, or an unsubstituted, mono-, di- or tri-substituted phenyl or heterocyclic moiety such, for example, as pyridyl, furyl, pyrroloyl, thienyl or pyrazinyl, preferably a furyl or substituted furyl group.

When R_4 represents a substituted phenyl group, the substituent(s) may be on any of the five available positions of the benzene ring and any two or more substituents may be the same or different. When R_4 represents a substituted furyl group, the substituent(s) may be on any of the three available positions and any two or more substituents may be the same or different.

Suitable substituents of such phenyl and heterocyclic, especially of phenyl, groups are halogen atoms, straight and branched chain alkyl groups having 1 to 4 carbon atoms, straight and branched chain alkyl groups having 1 to 4 carbon atoms, alkoxy groups having 1 to 4 carbon atoms, and trifluoromethyl, nitro, phenyl, sulfamoyl and hydroxy groups. Suitable furyl substituents are halo, preferably bromo groups and alkyl groups having from 1 to 4 carbon atoms, preferably methyl groups. Preferably the furyl group is unsubstituted or monosubstituted.

Of the above indole compounds, those where n represents 1 and X represents a hydrogen atom, including where R_1 and R_2 each represents a methoxy group or, preferably, a hydrogen atom and R_3 represents a hydrogen atom or a methyl group, are preferred; of this group, the substituents where R_4 represents an unsubstituted or substituted furyl or phenyl group are the preferred compounds. Next, there should be mentioned the indole compounds where n represents O and X represents a hydrogen atom and R_1, R_2, R_3 and R_4 have the meanings given above, preferably where R_1 and R_2 each represents a hydrogen and R_3 represents a hydrogen atom or a methyl group, and, more especially, where R_4 represents an unsubstituted or substituted furyl or unsubstituted or substituted phenyl group.

There should also be mentioned compounds wherein R_4 represents a methyl, benzhydryl, cyclohexyl, norbornyl, adamantyl or isonicotinyl group, or a group of the general formula



wherein R_5, R_6, R_7, R_8 and R_9, any two or more of which may be the same or different, each represents a hydrogen atom or a halogen atom having a molecular weight less than 80, or a straight or branched alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms or a trifluoromethyl, phenyl, sulphamoyl, nitro or hydroxy group.

Examples of the compounds of the invention are:

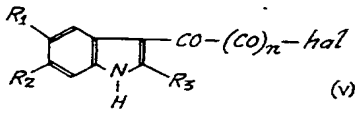
3-[2-(4-aminopiperazin-1-yl)ethyl]indole;
3-[2-(4-benzamidopiperazin-1-yl)ethyl]indole;
3-{2-[4-(3,4,5-trimethoxybenzamido)piperazin-1-yl]ethyl}indole;

3-[2-(4-*p*-fluorobenzamidopiperazin-1-yl)ethyl]indole;
3-[2-(4-*t*-butylbenzamidopiperazin-1-yl)ethyl]indole;
3-[2-(4-*p*-trifluoromethylbenzamidopiperazin-1-yl)ethyl]indole;
3-[1-hydroxy-2-(4-benzamidopiperazin-1-yl)ethyl]indole;
3-[2-(4-acetamidopiperazin-1-yl)ethyl]indole;
3-{2-[4-(2-furoylamidopiperazin-1-yl]ethyl}indole;
4-[2-(4-norbornanecarbonylamidopiperazin-1-yl)ethyl]indole;
3-[2-(4-benzamidopiperazin-1-yl)ethyl]-2-methylindole;
3-[2-(4-benzamidopiperazin-1-yl)ethyl]-5,6-dimethoxy-2-methylindole;
5,6-dimethoxy-3-[2-(4-p-fluorobenzamidopiperazin-1-yl)ethyl-2-methylindole;
3-(4-benzamidopiperazin-1-yl)methylindole;
3-[2-(4-*o*-methoxybenzamidopiperazin-1-yl)ethyl]indole;
4-[2-(4-*m*-methylbenzamidopiperazin-1-yl)ethyl]indole;
3-[2-(4-biphenylcarbonylamidopiperazin-1-yl)ethyl]indole;
3-{2-[4-(3,5-dimethoxybenzamido)piperazin-1-yl)ethyl}indole;
3-{2-[4-chloro-3-sulfamylbenzamidopiperazin-1-yl]ethyl}indole;
3-[2-(4-diphenylacetamidopiperazin-1-yl)ethyl]indole;
5,6-dimethoxy-2-methyl-3-[2-(4-p-trifluoromethylbenzamidopiperazin-1-yl)ethyl]-indole hydrochloride;
3-[2-(4-aminoperazin-1-yl)ethyl]-5,6-dimethoxy-2-propylindole and its hydrochloride;
3-[2-(4-benzamidopiperazin-1-yl)ethyl]-5-ethoxy-2-ethyl-6-methoxyindole;
3-{2-[4-(5-bromo-2-furoylamidopiperazin-1-yl)ethyl}indole;
3-{2-[4-(4-methyl-2-furoylamidopiperazin-1-yl)]ethyl}indole.

The compounds of the general formula I and their salts may be prepared by methods known *per se*.

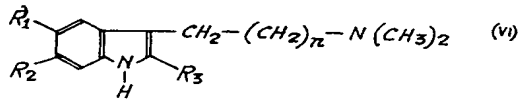
Thus, a compound of the general formula I or a salt thereof may be prepared by

a) reacting an indole of the general formula



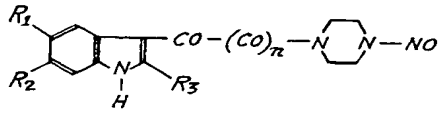
(V)

or



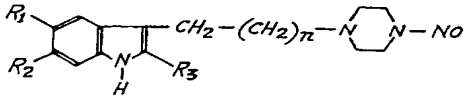
(VI)

wherein R_1, R_2, R_3 and n have the meanings given above and hal represents a fluorine, chlorine or bromine atom, with N-nitroso-piperazine to give a compound of the general formula



(VII)

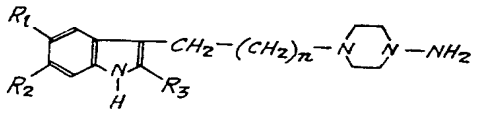
or



(VIII),

and

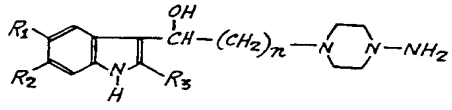
b) i) reducing the compound of the general formula VII or VIII to give a compound of the general formula



(IIIa)

or

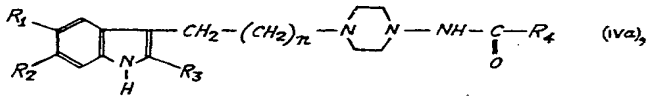
ii) partially reducing a compound of the formula VII to give a compound of the general formula



(IIIb)

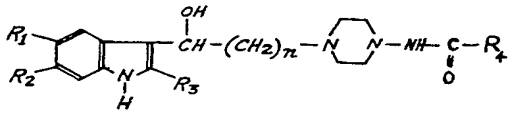
and, if desired,

c) acylating the compound of the general formula IIIa or IIIb to give a compound of the general formula



(ivα),

or



(ivβ).

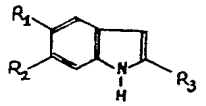
In the reaction step (bi), the reduction is suitably carried out with an alkali metal hydride in an inert solvent.

In the reaction step (bii), the reduction is suitably carried out with an alkali metal hydride in an inert solvent having a low boiling point, at reflux temperature or below. In this reaction, preferably $n=1$.

More especially, the partial reduction in reaction step (bii) is carried out in an inert solvent having a boiling point in the range of from 34 to 66°C, especially tetrahydrofuran or ether. Preferably, the alkali metal hydride used is lithium aluminium hydride.

In the reaction step (c), the acylation is suitably carried out with an acyl halide of the general formula R_4CO-hal, wherein R_4 has the meaning given above and hal represents a fluorine, chlorine or bromine atom, especially a chlorine atom, or an acid of the general formula R_4COOH, or an acid anhydride of the general formula $R_4—CO—O—CO—R_4'$, wherein R_4 and R_4' may be the same or different, and have the meaning given above for R_4.

The compound of the general formula V may be prepared by reaction of a compound of the general formula



(ix)

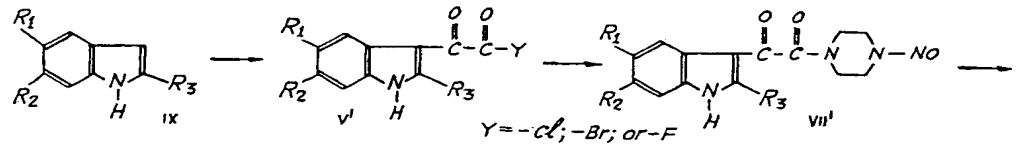
with an oxalyl halide. The compound of the formula V may be prepared *in situ* by reacting an acid sensitive indole and a hydrogen halide binder, e.g. potassium carbonate or triethylamine, in an immiscible solvent mixture, e.g. for 5,6-dimethoxy-2-indole a mixture of chloroform and water, with an oxalyl halide at a temperature in the range of from −10 to 50°C.

The compound of the general formula VIII may be 3-(4-nitrosopiperazin-1-yl)-methylindole, prepared by refluxing a mixture of gramine and nitrosopiperazine.

For example, the reaction schemes shown below in Figs. 1 to 3 illustrate the preparation of compounds of the general formulae III and IV, wherein

$n=1$ and X=H (Fig. 1),
$n=1$ and X=OH (Fig. 2), and
$n=0$ and X=H (Fig. 3).

Fig.1.



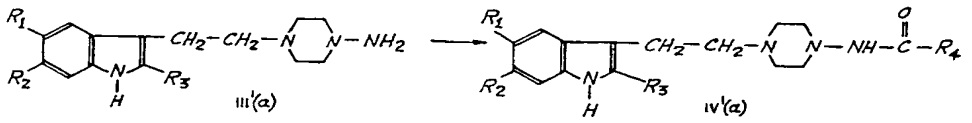


Fig.2.

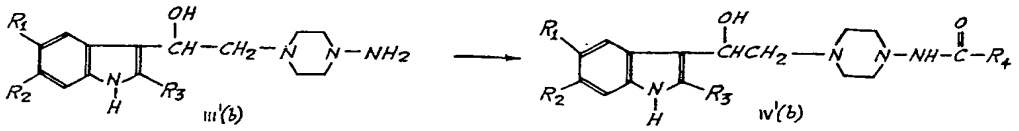
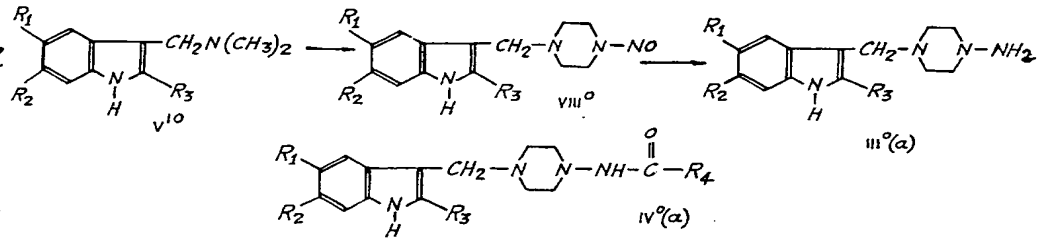


Fig.3.



Thus, for example, a 3-[2-(4-aminopiperazin-1-yl)ethyl]indole of the formula III'(a) and a 3-[2-(4-acylaminopiperazin-1-yl)ethyl]indole of the formula IV'(a), wherein R_1, R_2, R_3 and R_4 have the meanings given above, may be prepared by the following sequence designated as Method A and shown in Figure 1.

Starting with a substituted indole of the formula IX known in the literature, a 3-indolyl)glyoxalyl halide of the formula V' may be prepared by the method of Speeter *et al.*, J. Am. Chem. Soc., *76*, 6209 (1954).

The intermediate so prepared may be reacted with N-nitrosopiperazine preferably at a temperature in the range of from −10° to 100°C to give the 3-[1-(indol-3-yl-glyoxyloyl)-4-nitropiperazine of the formula VII'.

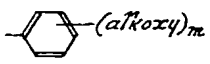
This reaction may or may not be carried out in a solvent or mixture of solvents. An added inorganic base such, for example, as potassium carbonate, or an organic base such, for example, as potassium carbonate, or an organic base such, for example, as triethylamine, may be used to bind the hydrogen halide liberated during the course of the reaction; and added base is optional because N-nitrosopiperazine itself can serve as the hydrogen ion acceptor.

Preferably, the reaction is carried out by adding the 3-(indolyl)glyoxalyl halide to a chloroform and water mixture containing the N-nitrosopiperazine and potassium carbonate while maintaining the temperature in the range of from 20 to 25°C over a span of from 1 minute to 60 minutes. This affords the crude indole product of the formula VII' in a nearly quantitative yield. With certain acid sensitive indoles, such, for example, as when R_1 and R_2 represents a methoxy group and R_3 represents a methyl group, it may be advantageous to combine the first two steps of this method in one reaction vessel without isolating the sensitive intermediate of the formula V'. For example, a mixture of 5,6-dimethoxy-2-methylindole and potassium carbonate in chloroform is treated with oxalyl chloride at −5°C and the resulting glyoxalyl chloride is reacted *in situ* with N-nitrosopiperazine to produce the intermediate of the formula VII'.

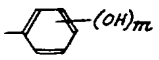
Reduction of the 3-(indolyl)glyoxamide of the formula VII' with an alkali metal hydride for a half hour to 24 hours, produces the 3-[2-(4-aminopiperazin-1-yl)-ethyl]indole of the formula III'(a). This reduction may be carried out in an organic solvent which is inert under the conditions of the reaction, for example in ether, tetrahydrofuran or 1,2-dimethoxyethane and suitably at a temperature in the range of from −10°C to the boiling point of the solvent.

In a preferred embodiment of the reaction, lithium aluminum hydride is used as the reducing agent and 1,2-dimethoxyethane is the solvent, and the mixture is refluxed to produce a nearly quantitative yield of a compound of the formula III'(a).

Acylation of the 3-[2-(4-aminopiperazin-1-yl)ethyl]indole with a reactive derivative of an acid of the general formula R_4COOH, wherein R_4 has the meaning given above, for from 5 minutes to 24 hours by a method known in the art produces the 3-[2-(4-acylaminopiperazin-1-yl)ethyl]indole compound of the formula IV'(a). Preferably, an acid halide or acid anhydride is used in this acylation. When the above is 3-[2-(4-acylaminopiperazin-1-yl)ethyl]indole, wherein R_4 represents



and m represents the integer 1, 2 or 3, these alkoxy groups may be dealkylated by methods known in the art to produce a



group.

A 3-[1-hydroxy-2-(4-aminopiperazin-1-yl)ethyl]indole of the formula III'(b) and a 3-[1-hydroxy-2-(4-acylaminopiperazin-1-yl)ethyl]indole of the formula IV'(b), wherein R_1, R_2, R_3 and R_4 have the meanings given above, may be prepared by the following sequence designated as Method B and shown in Figure 2.

When the aforementioned reduction of a glyoxamide of the formula VII' with an alkali metal hydride is carried out in a lower boiling inert solvent, either at reflux temperature or below, the reduction is incomplete and a compound of the formula III'(b) is produced. This may be separated from the fully reduced intermediate of the formula III'(a), also produced in the reaction, by crystallisation or other methods known in the art. One preferred system utilises lithium aluminum hydride as the alkali metal hydride and tetrahydrofuran (b.p. 65—67°C) as the inert solvent.

Acylation as previously described in Method A takes place selectively at the amino group to yield the 3-[1-hydroxy-2-(4-acylaminopiperazin-1-yl)ethyl]indole of the formula IV'(b).

A 3-(4-aminopiperazin-1-yl) methylindole of the formula III°(a) and a 3-(4-acylaminopiperazin-1-yl) methylindole of the formula IV°(a), wherein R_1, R_2, R_3 and R_4 have the meanings given above, may be prepared by the following sequence designated as Method C and shown in Figure 3.

A 3-dimethylaminomethylindole is allowed to react with N-nitrosopiperazine suitably in an inert solvent for 1 to 48 hours to produce the 3-(4-nitrosopiperazin-1-yl) methylindole in high yield. A preferred embodiment utilises toluene as the inert solvent at refluxing conditions for 1 to 2 days.

Reduction with an alkali metal hydride in an appropriate inert solvent produces the compound of the formula III°(a) illustrated in Figure 3. Preferably, this reduction is effected with lithium aluminum hydride in 1,2-dimethoxyethane by refluxing for from 0.5 hours to 6 hours.

Acylation as previously described with respect to Method A also produces the 3-(4-acylaminopiperazin-1-yl) methylindole of formula IV°(a) as illustrated in Figure 3.

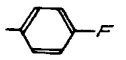
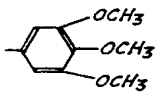
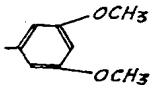
An acid addition salt of the 3-(4-amino) and the 3-(4-acyl-aminopiperazin-1-yl) alkylindole may be prepared according to well known procedures. Representative of such salts are those formed with mineral acids, such, for example, as the hydrochloride, hydrobromide, sulphate and phosphate and the organic acid salts, such, for example, as the maleate, oxalate, succinate, pamoate and *p*-toluenesulphonate.

The compounds of the formulae III and IV and their physiologically tolerable salts are useful as antihypertensive agents due to their ability to depress blood pressure in mammals. Antihypertensive activity was measured in the spontaneous hypertensive rat by the indirect tail cuff method described in A. Schwartz, Ed *Methods in Pharmacology*, Vol. I, page 135, Appleton-Century Crofts, New York, New York, 1971.

In a standard 3 day test, according to this procedure, systolic blood pressure readings were made at 0 time (control) on days 1 and 3. Dosing was orally at 100 mg/kg at 0 hour on days 1, 2 and 3 on groups of 6 animals per test. Activity was determined by comparison of the treated host's blood pressure values with the 0 time (control) blood pressure readings. A value of −15 mm Hg or more is considered significant.

The antihypertensive activity in this test of some of the compounds of the invention is illustrated in Table I.

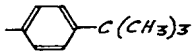
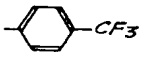
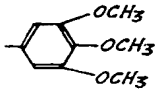
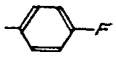
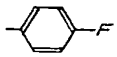
TABLE I

Compound of the General Formula						Day 1	Day 3
R_1+R_2	R_3	X	n	Z	R_4	mm Hg	mm Hg
H	H	H	1	$C-R_4$ (=O)		-24	-56
H	H	H	1	$C-R_4$ (=O)		-56	-57
H	H	H	1	$C-R_4$ (=O)		-63	-70
H	H	H	1	$C-R_4$ (=O)		-58	-64
H	H	H	1	$C-R_4$ (=O)		-53	-42
H	H	H	1	$C-R_4$ (=O)	$-CH_3$	-32	-40
H	H	OH	1	$C-R_4$ (=O)		-30	-33
H	CH_3	H	1	$C-R_4$ (=O)		-39	-37
H	H	H	1	$C-R_4$ (=O)		-46	-111
H	H	H	1	H	–	-36	-46
H	CH_3	H	1	H	–	-59	-31

Z is an acyl moiety or hydrogen atom as indicated.

Compounds of the formula I and their physiologically tolerable salts are also useful as tranquilising agents because of their depressant effects on the central nervous system. These tranquilising effects were measured according to the mouse observation procedure of S. Irwin, Psychopharmacologia, *9*, 259 (1966). In this test, male mice (type COBS) were dosed orally with the drug and its effects on behaviour and reflex depression, together with muscle relaxation, were determined by the degree of deviation from control scores. The overall result for 3 animals in each category for some compounds of this invention is expressed in terms of the minimum effective dose (MED) and is illustrated in Table II.

TABLE II

Compound of the General Formula						MED
R_1+R_2	R_3	X	n	Z	R_4	(mg/kg body weight)
H	H	H	1	C–R_4 ‖ O		75
H	H	H	1	C–R_4 ‖ O		75
H	H	H	1	C–R_4 ‖ O		37
H	H	H	1	C–R_4 ‖ O		40
H	H	H	1	C–R_4 ‖ O	$-CH_3$	75
H	CH_3	H	1	C–R_4 ‖ O		40
CH_3O	CH_3	H	1	C–R_4 ‖ O		75
CH_3O	CH_3	H	1	C–R_4 ‖ O		75
H	H	H	1	H	–	40

Z is an acyl moiety or hydrogen atom as indicated.

Compounds of the formula I having, for example, Z = —COR_4, and their physiologically tolerable salts, are suitably administered at a dose in the range of from 0.1 to 100 mg/kg body weight. They may be administered to a patient by various methods, for example orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intraveneously in the form of sterile solutions. The compound may be formulated and administered in the form of a physiologically tolerable addition salt for reasons of stability, convenience of crystallisation or increased solubility.

The active compounds of the present invention may be administered orally, for example with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers or chewing gum. These preparations advantageously should contain at least 0.5% of active compound, but the amount may be varied depending upon the particular form and may conveniently be in the range of from 4% to 70% of the weight of the dosage unit. Accordingly, the present invention provides a pharmaceutical preparation which comprises a compound of the general formula I or a physiologically tolerable salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier. The preparation may be in dosage unit form. The amount of active compound in such preparations is such that a suitable dosage will be obtained. Preferred dosage unit preparations, especially oral dosage unit preparations, contain from 0.1 to 100 milligrams of active compound.

The preparations, for example tablets, pills, capsules and troches, may also contain one or more of the following ingredients: a binder, such, for example, as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such, for example, as starch or lactose; a disintegrating agent such, for example as alginic acid, Primogel or corn starch; a lubricant such, for example, as magnesium stearate or Sterotex; a glidant such, for example, as colloidal silicon dioxide; and a sweetening agent such, for example, as sucrose or saccharin may be added or a flavouring agent, for example peppermint, methyl salicylate or orange flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such, for example, as a fatty oil. Other dosage unit forms may contain various other materials which modify the physical form of the dosage unit, for example as coatings. Thus tablets or pills may be coated with sugar, Shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent, and certain preservatives, dyes and colourings, and flavours. Materials used in preparing these various compositions should be pharmaceutically suitable and physiologically tolerable in the amounts used.

For parenteral administration, the carrier or excipient may be sterile, parenterally acceptable liquid; e.g. water or a parenterally acceptable oil, e.g. arachis oil contained in ampules.

The following Examples illustrate the invention.

Example 1.

3-[2-(4-Aminopiperazin-1-yl)ethyl]indole

a) To a solution of 13.6 (0.096 mol) of potassium carbonate in 60 ml of water is added a solution of 8.06 g (0.070 mol) of N-nitrosopiperazine in 60 ml of chloroform. The two phases are stirred vigorously while 12.4 g (0.060 mol) of indole-3-glyoxyl chloride is introduced in portions for 15 minutes while maintaining the reaction temperature at 20 to 25°C. The resultant gummy mixture is stirred for an additional 2 hours and then 50 ml of diethyl ether is added in portions. The gummy solid is thereby crystallised, stirred for an additional 15 minutes, and the crystalline product is filtered, washed with water, then with ethanol (2 × 25 ml) and dried to produce crystals of 1-(indol-3-ylglyoxyloyl)-4-nitrosopiperazine. This material is recrystallised from DMF (dimethylformamide) and water to produce pure crystals having a m.p. 223—225°C.

Analysis:

Calculated for $C_{14}H_{14}N_4O_3$:	58.74% C;	4.93% H;	19.57% N
Found:	58.77% C;	5.01% H;	19.66% N.

b) To a stirred mixture of 9.0 g of lithium aluminium hydride in 400 ml. of 1,2-dimethoxyethane is added 10.52 g (0.037 mol) of 1-(indol-3-ylglyoxyloyl)-4-nitrosopiperazine slowly to maintain reaction temperature below 35°C. After all the material is added, the mixture is refluxed for 14—16 hours. The reaction mixture is cooled to −5°C and a solution of 50 ml. of water and 50 ml. of 1,2-dimethoxyethane is slowly added while maintaining the temperature below 15°C. Another 50 ml. of water is added, and the mixture is then filtered. The solvent is removed from the filtrate and the residual solid is recrystallised from benzene, producing the pure crystals of 3-[2-(4-aminopiperazin-1-yl)ethyl]indole, m.p. 115—117°C.

Analysis:

Calculated for $C_{14}H_{20}N_4$:	68.82%; C,	8.25% H;	22.93% N
Found:	68.70% C;	8.17% H;	22.55% N.

Example 2.

3-[2-(4-Aminopiperazin-1-yl)ethyl]-2-methylindole

a) To a solution of 41.4 g (0.30 mol) of potassium carbonate in 300 ml. of water is added a solution of 38.1 g (0.33 mol) of N-nitrosopiperazine in 300 ml of chloroform. The two phases are stirred vigorously while 66.4 g (0.30 mol) of 2-methyl-indole-3-glyoxyl chloride is introduced in portions for 30 minutes. The resultant mixture is stirred for an additional 0.5 hour and then 300 ml of diethyl ether is added in portions. The product is filtered, washed with water, then with ethanol and dried to afford crystals of 1-(2-methylindole-3-ylglyoxyloyl)-4-nitrosopiperazine. Purification is accomplished by recrystallisation from DMF and water to produce crystals having a m.p. 231°—232°C.

Analysis:

Calculated for $C_{15}H_{15}N_4O_3$:	59.99% C;	5.04% H;	18.66% N
Found:	60.36% C;	5.28% H;	18.76% N.

b) To a stirred mixture of 9.0 g of lithium aluminium hydride in 400 ml of 1,2-dimethoxyethane is added 10.52 g (0.35 mol) of 1-(2-methylindol-3-ylglyoxyloyl)-4-nitrosopiperazine slowly to maintain reaction temperature below 35°C. After all the material is added, the mixture is refluxed for 14—16 hours. The reaction mixture is cooled to −5°C and a solution of 50 ml of water and 50 ml of 1,2-dimethoxyethane is slowly added while maintaining the temperature below 15°C. Another 50 ml of water is added. The mixture is then filtered, the solvent is removed, and the residual solid is recrystallised from hot benzene, producing the pure crystals of 3-[2-(4-amino-piperazin-1-yl)ethyl]-2-methylindole, m.p. 118—120°C.

Analysis:

Calculated for $C_{15}H_{22}N_4$:	71.08% C;	8.21% H;	20.72% N
Found:	71.11% C;	8.28% H;	20.75% N.

Example 3.

3-(4-Aminopiperazin-1-yl) methylindole

a) A mixture of 34.8 g (0.22 mol) of gramine and 23.0 g (0.20 mol) of nitroso-piperazine in 700 ml of toluene is refluxed while stirring under nitrogen for 48 hours. The reaction solution is then concentrated under reduced pressure until a precipitate appears and then is cooled to 0°C and is filtered. The product is washed with cold toluene and dried to produce crystals of 3-(4-nitrosopiperazin-1-yl)methylindole. This product is recrystallised from toluene to yield pure plates, m.p. 116—118°C.

Analysis:

Calculated for $C_{13}H_{16}N_4O$:	63.92% C;	6.60% H;	22.93% N
Found:	63.84% C;	6.64% H;	23.06% N.

b) To a stirred mixture of 10.5 g of lithium aluminium hydride in 100 ml of 1,2-dimethoxyethane is added slowly 38 g (0.16 mol) of 3-(4-nitrosopiperazin-1-yl) methylindole while maintaining the temperature below 35°C. After total addition of the material, the mixture is refluxed for four hours. The reaction mixture is cooled to 0°C and a solution of 50 ml of water and 50 ml of 1,2-dimethoxyethane is added slowly maintaining the temperature below 20°C and an additional 50 ml of water is added. The mixture is filtered and the solvent is removed from the filtrate. The residual solid is recrystallised from ethanol and water (2:1) to produce pure flakes of 3-(4-amino-piperazin-1-yl) methylindole, m.p. 147—149°C.

Analysis:

Calculated for $C_{13}H_{18}H_4$:	67.80% C;	7.88% H;	24.33% N
Found:	67.69% C;	7.94% H;	24.28% N.

Example 4.

3-[2-(4-Benzamidopiperazin-1-yl)ethyl]indole

A stirred solution of 6.13 g (0.025 mol) of 3-[2-(4-aminopiperazin-1-yl)ethyl]-indole as obtained in Example 1 and 3.54 g (0.035 mol) of triethylamine in 75 ml of chloroform is cooled to 0°C with exclusion of moisture. A solution of 4.20 g (0.03 mol) of benzoyl chloride in 5 ml of chloroform is added slowly for 30 minutes, while maintaining the temperature at 0—5°C. The product starts crystallising after half the material is added; after total addition, the mixture is stirred for two hours at ambient temperature. Crystalline form is improved by the addition of 75 ml of 10% sodium hydroxide and 100 ml of diethyl ether and stirring for an additional 15 minutes. The product is filtered, washed with water, then diethyl ether and dried. This product is recrystallised twice from methanol, then from DMF and water to give powdery crystals of 3-[2-(4-benzamidopiperazin-1-yl)ethyl]indole m.p. 227—229°C., as the monohydrate.

Analysis:

Calculated for $C_{21}H_{24}N_4O.H_2O$:	68.83% C;	6.60% H;	15.29% N
Found:	69.30% C;	6.67% H;	15.31% N.

Example 5—23.

By following the manipulative procedure described in Example 4, substituting for the benzoyl chloride, the appropriate mono-, di- or tri-substituted benzoyl halide, there are produced the 3-[2-(4-substituted -benzamidopiperazin-1-yl)ethyl]indoles, listed in Table III.

TABLE III

Ex	Substituents	Recryst'n Solvent	Empirical Formula	M.P. °C	Analysis Cal'd. %C	%H	%N	Found %C	%H	%N
5	*p*-Methyl	EtOH/H_2O	$C_{22}H_{26}N_4O$	231–234	72.90	7.23	15.46	72.69	7.22	15.51
6	*o*-Methyl	MeOH	$C_{22}H_{26}N_4O$	211–213	72.90	7.23	15.46	73.08	7.38	15.55
7	*m*-Methyl	DMF/H_2O	$C_{22}H_{26}N_4O$	201–203	72.90	7.23	15.46	72.79	7.46	15.37
8	*p*-Methoxy	DMF/H_2O	$C_{22}H_{26}N_4O_2$	210–215 dec.	69.82	6.92	14.80	69.54	6.86	14.79
9	*o*-Methoxy	MeOH	$C_{22}H_{26}N_4O_2$	230–232	69.82	6.92	14.80	69.62	7.06	14.73
10	*m*-Methoxy	DMF/H_2O	$C_{22}H_{26}N_4O_2$	220–222	69.82	6.92	14.80	69.80	6.96	14.75
11	*p*-Ethoxy	EtOH/H_2O	$C_{23}H_{28}N_4O_2$	202–204	70.38	7.19	14.27	70.76	7.10	14.08
12	*p*-Butoxy	EtOH/H_2O	$C_{25}H_{32}N_4O_2$	200–202	71.40	7.67	13.32	71.61	7.62	13.46
13	[3,5-Dimethoxy]	EtOAc	$C_{23}H_{28}N_4O_3$	195–197	67.63	6.91	13.72	67.61	6.85	13.56
14	[3-Methoxy-4-Methyl]	CH_3CN	$C_{23}H_{28}N_4O_2$	222–225	70.38	7.19	14.27	69.98	7.03	14.50
15	[3,4,5-Trimethoxy]	EtOH/H_2O	$C_{24}H_{30}N_4O_4$	161–163	65.73	6.90	12.78	65.51	6.90	12.82
16	*p*-*tert*-Butyl	EtOH/H_2O	$C_{25}H_{32}N_4O$	209–212	74.22	7.97	13.85	74.06	7.80	13.77
17	*m*-Trifluoromethyl	DMF/H_2O	$C_{22}H_{23}F_3N_4O$	194–196	63.45	5.57	13.45	62.77	5.54	13.30
18	*p*-Trifluoromethyl	EtOH/H_2O	$C_{22}H_{23}F_3N_4O$	216–219	63.45	5.57	13.45	63.25	5.57	13.48
19	*p*-Chloro	DMF/H_2O	$C_{21}H_{23}ClN_4O$	256–259 dec.	65.88	6.05	14.63	66.13	5.95	14.85
20	*p*-Fluoro	DMF/H_2O	$C_{21}H_{23}FN_4O$	256–259 dec.	68.83	6.33	15.29	68.90	6.31	15.44
21	*o*-Fluoro	DMF/H_2O	$C_{21}H_{23}FN_4O$	185–187	68.83	6.33	15.29	68.66	6.48	15.43
22	*p*-Nitro	EtOH/H_2O	$C_{21}H_{23}N_5O_3$	205–208	64.11	5.89	17.80	64.43	5.85	17.65
23	4-Chloro-3-Sulphamoyl	EtOH/H_2O	$C_{21}H_{24}ClN_5O_3S$	135–138	54.60	5.24	15.16	54.87	5.06	15.02

Example 24.

3-[2-(4-*p*-Hydroxybenzamidopiperazin-1-yl)ethyl]indole

To a stirred mixture of 2.5 g (0.0066 mol) of 3-[2-(4-*p*-methoxybenzamidopiperazin-1-yl)ethyl]indole, Example 8, in 25 ml of dry 2,4,6-collidine is added 5.0 g of LiI (exothermic t→30°C). The mixture is heated to reflux under nitrogen for 4 hours. The reaction is cooled, acidified with 3N HCl, stirred for 30 minutes and then carefully made basic with sodium carbonate. The oily collidine is extracted with diethyl ether and the aqueous layer stripped off in an evaporator. The solid product is triturated with water, filtered, and washed well with water. This material is then dissolved in 10 ml of methanol, absorbed on to a column of 500 g of silica gel made up in benzene, and chromatographed. The fractions eluted with 2% methanol in chloroform are combined and the solvent removed leaving a solid. The solid is recrystallised from an ethanol-water mixture to give a pure product, m.p. 190—192°C, of 3-[2-(4-*p*-hydroxybenzamidopiperazin-1-yl)ethyl]indole.

Analysis:

Calculated for $C_{21}H_{24}N_4O_2$:	69.24% C;	6.59% H;	15.37% N
Found:	69.41% C;	6.42% H;	15.14% N.

Example 25.

3-[2-(4-Biphenylcarbonylamidopiperazin-1-yl)ethyl]indole

A stirred solution of 6.13 g (0.025 mol) of 3-[2-(4-aminopiperazin-1-yl)ethyl]-indole obtained according to Example 1, and 3.54 g (0.035 mol) of triethylamine in 100 ml of chloroform is cooled to −5°C. Then 6.25 g (0.03 mol) of biphenylcarbonyl chloride is added portionwise for 15 minutes maintaining the reaction temperature at 0—5°C. After total addition, the reaction mixture is stirred at ambient temperature for 3 hours. Then 50 ml of 10% sodium hydroxide followed by 100 ml of diethyl ether is added to promote crystallisation. The product is filtered, washed well with water and dried. This is recrystallised twice from ethanol and water to give pure white flakes of 3-[2-(4-biphenylcarbonylamidopiperazin-1-yl)ethyl]indole, m.p. 230—233°C.

Analysis:

Calculated for $C_{27}H_{29}N_4$:	76.39% C;	6.65% H;	13.20% N
Found:	76.47% C;	6.66% H;	13.01% N.

Examples 26—30.

By following the manipulative procedure described in Example 25, substituted for the biphenyl carbonyl chloride the appropriate carbonyl chloride, novel compounds listed in Table IV are produced.

TABLE IV

Ex	R_4	Recryst'n Solvent	Empirical Formula	M.P. °C.	Analysis Calculated %C	%H	%N	Found %C	%H	%N
26	Cyclohexanecarbonyl	EtOH/H_2O	$C_{21}H_{29}N_4O$	205–208	71.15	8.53	15.80	70.94	8.57	16.03
27	2-Furoyl	EtOH/H_2O	$C_{19}H_{22}N_4O_2$	201–203	67.44	6.55	16.56	67.22	6.57	16.49
28α	Norbornanecarbonyl	EtOH/H_2O	$C_{22}H_{30}N_4O$	178–181	72.10	8.25	15.29	71.94	8.59	15.09
29	Adamantanecarbonyl	EtOH/H_2O	$C_{25}H_{34}N_4O$	214–216	73.86	8.43	13.78	73.62	8.13	13.40
30	Diphenylacetyl	EtOH/H_2O	$C_{28}H_{30}N_4O$	162–163	76.58	7.11	12.75	76.46	6.94	12.85

α–Hexane is used to promote crystallisation, instead of ether.

Example 31.

3-[2-(4-Isonicotinoylamidopiperazin-1-yl)ethyl]indole

A stirred solution of 6.13 g (0.025 mol) of 3-(4-aminopiperazin-1-yl)ethyl]indole, Example 1, and 3.54 g (0.035 mol) of triethylamine in 100 ml. of chloroform is cooled to 0°C, with exclusion of moisture. Then 5.35 g (0.03 mol) of isonicotinoyl chloride is added portionwise for 15 minutes maintaining the reaction temperature at 0—5°C. After total addition, the reaction mixture is stirred for 24 hours at ambient temperature. Then 50 ml of 10% sodium hydroxide is added while stirring. The chloroform layer is separated, washed with water and dried. The solvent is evaporated and the residual solid is recrystallised twice from ethanol and water to give the pure product, 3-[2-(4-isonicotinoylamidopiperazin-1-yl)ethyl]indole, m.p. 227—229°C.

Analysis:

Calculated for $C_{20}H_{24}N_5O$: 68.75% C; 6.63% H; 20.04% N
Found: 68.72% C; 6.72% H; 20.02% N.

In addition, by following the manipulative procedure described in Example 31 above, substituting for isonicotinoyl chloride, nicotinoyl chloride, 4-methyl-2-furoyl chloride, and 2-pyrrolyl chloride, the following novel compounds are obtained:
3-[2-(4-nicotinoylamidopiperazin-1-yl)ethyl]indole;
3-{2-[4-(4-methyl-2-furoylamido)piperazin-1-yl]ethyl}indole; and
3-{2-[4-(2-pyrroylamido]piperazin-1-yl]ethyl}indole;
respectively.

Example 32.

3-[2-(4-*p*-Isopropylbenzamidopiperazin-1-yl)ethyl)indole hydrochloride

a) *p*-isopropylbenzaldehyde is oxidised to the corresponding benzoic acid by using potassium permanganate in sulphuric acid as the oxidising agent at low temperature. The acid is converted to the acid chloride using thionyl chloride with a trace of dimethylformamide as a catalyst to give *p*-isopropylbenzoyl chloride.

b) A stirred solution of 6.13 g (0.025 mol) of 3-[2-(4-aminopiperazin-1-yl)-ethyl]indole obtained according to Example 1, and 3.54 g (0.035 mol) of triethylamine in 75 ml of chloroform is cooled to 0°C, with exclusion of moisture. A solution of 5.57 g (0.03 mol) of *p*-isopropylbenzoyl chloride in 5 ml of chloroform is added dropwise over a 30 minute span, while maintaining a reaction temperature of 0—5°C. After total addition, the mixture is stirred at ambient temperature for two hours. Then 50 ml of 10% sodium hydroxide is added to the reaction and stirring is continued for 30 minutes. The chloroform layer is separated and concentrated under reduced pressure. The residual solid is converted to the hydrochloride salt by dissolving it in ethanol and adding an equal volume of hydrogen chloride in ether. The precipitated salt is recrystallised from isopropanol and ether to yield 3-[2-(4-*p*-isopropylbenzamido-piperazin-1-yl)ethyl]indole hydrochloride, m.p. 209—210°C.

Analysis:

Calculated for $C_{24}H_{30}NO$:HCl	67.51% C;	7.32% H;	13.12% N;	8.54% Cl
Found:	67.78% C;	7.30% H;	13.04% N;	8.49% Cl.

Example 33.

3-[1-Hydroxy-2-(4-benzamidopiperazin-1-yl)ethyl]indole

a) To a stirred mixture of 9.0 g of lithium aluminium hydride in 400 ml. of tetrahydrofuran is added 10.5 g (0.037 mol) of 1-indol-3-ylglyoxyloyl)-4-nitroso-piperazine, obtained according to Example 1 (a), while maintaining the reaction temperature below 35°C. After total addition of the material, the mixture is refluxed for 14—16 hours. In this lower boiling solvent, the reduction is incomplete and 3-[1-hydroxy-2-(4-aminopiperazin-1-yl)ethyl]indole and 3-[2-(4-aminopiperazin-1-yl)-ethyl]indole are produced. The partially reduced product is separated from the totally reduced material by crystallisation from ethanol to give pure crystals of 3-[1-hydroxy-2-(4-aminopiperazin-1-yl)ethyl]indole, m.p. 174—177°C.

Analysis:

Calculated for $C_{14}H_{20}N_4O$:	64.59% C;	7.74% H;	21.52% N
Found:	64.54% C;	7.84% H;	21.80% N.

b) To a stirred slurry of 8.60 g (0.0334 mol) of 3-[1-hydroxy-2-(4-amino-piperazin-1-yl)ethyl]indole in 50 ml of chloroform is added 4.55 g (0.045 mol) of triethylamine. The mixture is cooled to 0°C under a nitrogen atmosphere, and a solution of 5.64 g (0.040 mol) of benzoyl chloride in 10 ml of chloroform is introduced dropwise for 1 hour, while maintaining the reaction temperature at 0—5°C. The resulting mixture is stirred at 0°C for one hour, and at ambient temperature for another hour. The mixture is diluted with 150 ml of chloroform and then 100 ml of 10% sodium hydroxide. The mixture is stirred for 15 minutes and then filtered; the cake is washed well with water and dried to give a white solid. This product is recrystallised first from an ethanol and water mixture and then twice from DMF and water to give pure white crystals of 3-[1-hydroxy-2-(4-benzamidopiperazin-1-yl)-ethyl]indole, m.p. 211—213°C dec.

Analysis:

Calculated for $C_{21}H_{24}N_4O_2$:	69.21% C;	6.64% H;	15.37% N
Found:	69.00% C;	6.60% H;	15.28% N.

Example 34.

3-[2-(-Acetamidopiperazin-1-yl)ethyl]indole

A stirred solution of 7.34 g (0.03 mol) of 3-[2-(4-aminopiperazin-1-yl)ethyl]-indole obtained according to Example 1, and 6.12 g (0.06 mol) of acetic anhydride in 75 ml of benzene is heated to 50°C and is allowed to react for 2 hours; a fine white precipitate appears. The reaction mixture is then stirred at ambient temperature for two more hours. The product is filtered, washed with diethyl ether, and dried. The product is thereafter crystallised from an ethanol and water mixture (1:1) to give white crystals of 3-[2-(4-acetamidopiperazin-1-yl)ethyl]indole, m.p. 193—186°C.

Analysis:

Calculated for $C_{16}H_{22}N_4O$: 67.11% C; 7.74% H; 19.56% N
Found: 67.14% C; 7.85% H; 19.76% N.

Example 35.

3-[2-(4-Benzamidopiperazin-1-yl)ethyl]-2-methylindole

A stirred solution of 7.70 g (0.03 mol) of 3-[2-(4-aminopiperazin-1-yl)ethyl]-2-methylindole obtained according to Example 2, and 3.54 g (0.035 mol) of triethylamine in 75 ml of chloroform is cooled to −5°C with exclusion of moisture. Then a solution of 4.20 g (0.03 mol) of benzoyl chloride in 5 ml of chloroform is added slowly for a half hour, maintaining the reaction temperature at 0—5°C. After total addition, the solution is stirred for two hours at ambient temperature. Then 50 ml of sodium hydroxide followed by 50 ml of diethyl ether is added to promote crystallisation. After thirty minutes an additional 75 ml of diethyl ether is introduced to improve the crystalline form. The product is filtered, washed with water, then diethyl ether and dried. The product is recrystallised twice from a DMF and water mixture to give white crystals of 3-[2-(4-benzamidopiperazin-1-yl)ethyl]-2-methylindole, m.p. 130—133°C.

Analysis:

Calculated for $C_{22}H_{26}N_4O$: 72.90% C; 7.23% H; 15.46% N
Found: 72.91% C; 7.51% H; 15.82% N.

Example 36 and 37.

By following the manipulative procedure described in Example 35, but substituting for benzoyl chloride the appropriate substituted benzoyl chloride, the 3-[2-(4-substituted benzoyl chloride, the 3-[2-(4-substituent benzamidopiperazin-1-yl)ethyl]-2-methylindole listed in Table V is produced. In these two Examples, the crude crystalline product is not washed initially with water; it is only washed with diethyl ether.

TABLE V

Ex	Substituent	Recryst'n Solvent	Empirical Formula	M.P. °C.	Analysis Calc'd. %C	%H	%N	Found %C	%H	%N
36	*p*-Fluoro	DMF/H_2O	$C_{22}H_{25}FN_4O$	222–224	69.45	6.62	14.73	69.69	6.74	15.01
37	*p*-Nitro	EtOH/H_2O	$C_{22}H_{25}N_5O_3$	136–139	64.85	6.18	17.19	64.58	6.03	17.07

Example 38.

3-[2-(4-Benzamidopiperazin-1-yl)ethyl]-5,6-dimethoxy-2-methylindole

a) A stirred mixture of 3.82 g (0.02 mol) of 5,6-dimethoxy-2-methylindole and 5.80 g (0.44 mol) of potassium carbonate in 50 ml of chloroform and 15 ml of water is cooled −5°C. Then 3.2 g (0.024 mol) of oxalyl chloride is added slowly, maintaining the reaction temperature at 0°C. The resulting mixture is stirred at room temperature for 10 minutes. Then 3.5 g (0.03 mol) of nitrosopiperazine is added over a 5 minute span. The reaction mixture turns red-purple and is stirred for an additional hour. To the solution is slowly added in portions 250 ml of diethyl ether; the solution appears lighter and a tan precipitate forms. After stirring for one hour, the product is filtered, washed well with water and dried. This product is recrystallised from a DMF and water mixture to give flakes of 1-(5,6-dimethoxy-2-methylindol-3-ylglyoxyloyl)-4-nitrosopiperazine m.p. 223—225°C.

Analysis:

Calculated for $C_{17}H_{20}N_4O_5$:	56.66% C;	5.59% H;	15.55% N
Found:	56.65% C;	5.61% H;	15.68% N.

b) To a stirred mixture of 9.0 g of lithium aluminium hydride in 400 ml of 1,2-dimethoxyethane is slowly added 11 g of 1-(5,6-dimethoxy-2-methylindol-3-yl-glyoxyloyl)-4-nitrosopiperazine while maintaining the temperature below 35°C. After total addition, the mixture is refluxed for 14—16 hours. The reaction mixture is then cooled to −5°C and a solution of 50 ml of water and 50 ml of 1,2-dimethoxyethane is slowly added keeping the temperature below 15°C, followed by an additional 50 ml of water. Upon filtration and removal of the solvent an amorphous foam of 3-[2-(4-aminopiperazin-1-yl)ethyl]-5,6-dimethoxy-2-methylindole is obtained, which could not be solidified by crystallisation or salt formation. Infrared (IR) and nuclear magnetic resonance (NMR) analysis confirms the aforementioned structure.

c) A stirred mixture of 7.92 g (0.025 mol) of 3-[2-(4-aminopiperazin-1-yl)-ethyl]-5,6-dimethoxy-2-methylindole and 3.54 g (0.035 mol) of triethylamine in 75 ml. of chloroform is cooled to −5°C, with the exclusion of moisture. Then a solution of 4.20 g (0.03 mol) of benzoyl chloride is 6 ml of chloroform is added dropwise over a 30 minute span, while maintaining a temperature of 0—5°C. After total addition, the mixture is stirred at ambient temperature for two hours. The 50 ml of 10% sodium hydroxide is added, followed by 50 ml of diethyl ether to promote crystallisation. After stirring for 15 minutes, another 100 ml. of ethyl ether is added to improve crystallisation form. The product is filtered, washed well with water, then diethyl ether and dried. This crystalline product is recrystallised twice from DMF and water mixture to give pure needles of 3-[2-(4-benzamidopiperazin-1-yl)ethyl]-5,6-dimethoxy-2-methylindole, m.p. 128—131°C.

Analysis:

Calculated for $C_{24}H_{30}N_4O_3$	68.22% C;	7.16% H;	13.26% N
Found:	68.03% C;	7.14% H;	13.12% N.

Example 39.

5,6-Dimethoxy-3-[2-(4-p-fluorobenzamidopiperazin-1-yl)ethyl]-2-methylindole

A stirred solution of 7.92 g (0.025 mol) of 3-[2-(4-aminopiperazin-1-yl)ethyl]-5,6-dimethoxy-2-methylindole, obtained according to Example 38 (b), and 3.54 g (0.035 mol) of triethylamine in 75 ml. of chloroform is cooled to −5°C with exclusion of moisture. A solution of 4.75 g (0.03 mol) of *p*-fluorobenzoyl chloride in 5 ml of chloroform is slowly added over a 30 minute span, while maintaining the reaction temperature at 0.—5°C. After total addition, the mixture is stirred for two hours at ambient temperature. Then 50 ml of 10% sodium hydroxide followed by 50 ml of diethyl ether is added to promote crystallisation. The mixture is stirred for 30 minutes and an additional 75 ml of diethyl ether is added to improve the crystalline form. The product is filtered, washed with water, ethyl ether, and then dried. The product is recrystallised twice from an ethanol and water mixture to give white crystals of 5,6-dimethoxy-3-[2-(4-*p*-fluorobenzamidopiperazin-1-yl)ethyl]-2-methylindole, m.p. 116—119°C.

Analysis:

Calculated for $C_{24}H_{29}FN_4O_3$:	64.43% C;	6.64% H;	12.71% N
Found:	64.29% C;	6.59% H;	12.50% N.

Example 40.

5,6-Dimethoxy-3-[2-(4-o-methoxybenzamidopiperazin-1-yl)ethyl]-2-methylindole Hydrochloride

A stirred solution of 7.92 g (0.025 mol) of 3-[2-(4-aminopiperazin-1-yl)ethyl]-5,6-dimethyl-2-methylindole, obtained according to Example 38 (b), and 4.54 g (0.035 mol) of triethylamine in 75 ml of chloroform is cooled to 0°C with exclusion of moisture. Then 5.12 g (0.03 mol) of *o*-anisoyl chloride dissolved in 5 ml of chloroform is added dropwise for a 30 minute span while maintaining the reaction temperature at 0—5°C. After total addition, the solution is stirred at ambient temperature for 3 hours. Then 50 ml of 10% sodium hydroxide is added and the mixture is stirred for 15 minutes. The chloroform layer is separated, and concentrated until a residue remains.

The above residue is dissolved in ethanol, a solution of hydrogen chloride in diethyl ether is introduced until the turbidity point is attained, and then ether is added with vigorous stirring. The product is filtered and washed well with ethyl ether. This product is recrystallised from isopropanol to give a white crystalline powder of 5,6-dimethoxy-3-[2-(4-o-methoxybenzamidopiperazin-1-yl)ethyl]-2-methylindole hydrochloride, m.p. 122—123°C, dec.

Analysis:

Calculated for $C_{25}H_{32}N_4O_4$:HCl: 62.69% C; 4.84% H; 11.69% N; 7.40% Cl
Found: 62.40% C; 4.60% H; 11.64% N; 7.38% Cl.

Example 41.

5,6-Dimethoxy-2-methyl-3-[2-(4-*p*-trifluoromethylbenzamidopiperazin-1-yl)ethyl]-indole Hydrochloride

By following the manipulative procedure in Example 40, substituting the *o*-anisoyl chloride as the acylating agent, *p*-trifluoromethylbenzoyl chloride, the pure product of 5,6-dimethoxy-2-methyl-3-[2-(4-*p*-trifluoromethylbenzamidopiperazin-1-yl)ethyl]-indole hydrochloride, m.p. 172—175°C is formed.

Analysis: Calculated for $C_{25}H_{29}F_3N_4O$:HCl:
60.66% C; 6.11% H; 11.32% N; 7.16% Cl; 11.52% F
Found: 60.32% C; 6.09% H; 11.38% N; 7.19% Cl; 11.55% F.

Example 42.

3-(4-Benzamidopiperazin-1-yl) methylindole

A stirred solution of 6.9 g (0.03 mol) of 3-(4-aminopiperazin-1-yl)methylindole obtained according to Example 3, and 4.05 g (0.04 mol) of triethylamine in 75 ml of chloroform is cooled to −5°C, with exclusion of moisture. A solution of 4.35 g (0.035 mol) of benzoyl chloride in 5 ml of chlorform is added dropwise over a fifteen minute span while maintaining a reaction temperature of 0—5°C. After total addition, the mixture is stirred at ambient temperature for 2 hours. Then 50 ml of 10% sodium hydroxide solution is added, followed by 50 ml of ethyl ether to promote crystallisation. The reaction mixture is stirred for another 30 minutes and an additional 50 ml of ether is added to improve the crystalline form. The product is filtered, washed well with water, then diethyl ether, and dried. This product is recrystallised twice from an ethanol and water mixture to give pure white flakes of 3-(4-benzamidopiperazin-1-yl)-methylindole, m.p.176—187°C.

Analysis:

Calculated for $C_{20}H_{21}N_4O$: 71.83% C; 6.63% H; 16.75% N
Found: 72.10% C; 6.53% H; 16.71% N.

Examples 43 and 44.

By following the manipulative procedure described in Example 42, wherein the acylating agent is the appropriate substituted benzoyl chloride, the 3-[4-(R_4-benzamido)piperazin-1-yl]methylindole listed in Table VI is produced.

TABLE VI

Ex	R_4 Substituent	Recryst'n Solvent	Empirical Formula	M.P. °C.	Analysis Calc'd. %C	%H	%N	Found %C	%H	%N
43	3,4,5-Trimethoxy	EtOH/H_2O	$C_{23}H_{28}N_4O_4$	206–208	65.08	6.65	13.20	65.15	6.45	13.10
44	*p*-Fluoro	EtOH/H_2O	$C_{20}H_{21}N_4FO$	206–208	68.16	6.01	15.89	68.15	6.03	15.79

Examples 45—47.

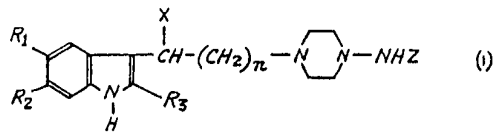
By following the manipulative procedure described in Example 31, substituting for isonicotinoyl chloride the appropriate carbonyl chloride, novel compounds listed in Table VII are produced.

TABLE VII

Ex	R_4 Substituent	Recryst'n Solvent	Empirical Formula	M.P. °C.	Analysis Calc'd. %C	%H	%N	Found %C	%H	%N
45	5-bromo-2-furoyl	EtOH/H_2O	$C_{19}H_{21}BrN_4O_2$	195–198	54.69	5.07	13.42	54.76	5.21	13.43
46	pyrazinoyl	Isopropanol	$C_{19}H_{23}N_6O$	195–197	64.97	6.54	23.91	64.88	6.44	23.68
47	2-thienyl	EtOH/H_2O	$C_{19}H_{22}N_4OS$	139–141	64.37	6.25	15.51	64.03	6.34	15.43

WHAT WE CLAIM IS:—

1. A compound of the general formula



(I)

wherein

X represents a hydrogen atom or hydroxy group,

n represents 0 or 1,

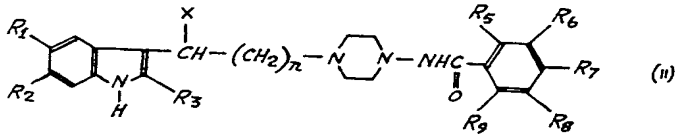
R_1 and R_2, which may be the same or different, each represents a hydrogen atom or an alkoxy group having 1 or 2 carbon atoms,

R_3 represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, and

Z represents a hydrogen atom or a group of the formula —CO—R_4, wherein R_4 represents an alkyl group having from 1 to 4 carbon atoms, a benzhydryl group, a cycloalkyl group having from 6 to 10 carbon atoms, a bridged cycloalkyl group having from 6 to 10 carbon atoms, an unsubstituted or substituted phenyl group or an unsubstited or substituted heterocyclic group.

2. A compound as claimed in claim 1, wherein R_4 represents a phenyl group which is unsubstituted or substituted by one or more of the same or different substituents selected from alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 4 carbon atoms, halogen atoms and trifluoromethyl, phenyl, sulphamoyl, nitro and hydroxy groups.

3. A compound as claimed in claim 2 of the general formula



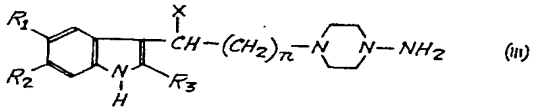
(II)

wherein X, n, R_1, R_2 and R_3 have the meanings given in claim 1, and R_5, R_6, R_7, R_8 R_9, any two or more of which may be the same or different, each represents a hydrogen, fluorine, chlorine or bromine atom or an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, or a trifluoromethyl, phenyl sulphamoyl, nitro or hydroxy group.

4. A compound as claimed in any one of claims 1 to 3, wherein R_4 represents a phenyl group which unsubstituted, mono-, di- or tri-substituted.

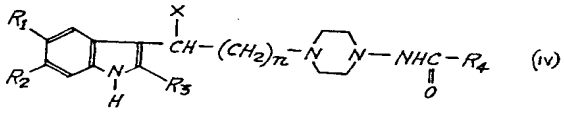
5. A compound as claimed in claim 1, wherein R_4 represents an unsubstituted or substituted pyridyl, furyl, pyrrolyl, thienyl or pyrazinyl group.

6. A compound of the general formula



(III)

or



(IV)

wherein X represents a hydrogen atom or hydroxy group; n represents 0 or 1; R_1 and R_2, which may be the same or different, each represents a hydrogen atom or an alkoxy group having 1 to 2 carbon atoms; R_3 represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms; and R_4 represents an alkyl group having from 1 to 4 carbon atoms, a benzhydryl group, a cycloalkyl group having from 6 to 10 carbon atoms, a bridged cycloalkyl group having from 6 to 10 carbon atoms, a phenyl group which is unsubstituted, mono- di- or tri-substituted by one or more of the same or different substituents selected from alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 4 carbon atoms, halogen atoms, and trifluoromethyl, phenyl, sulphamoyl, nitro and hydroxy groups, or represents an unsubstituted or substituted furyl, thienyl, pyrrolyl, pyrazinyl or pyridyl group.

7. A compound as claimed in claim 5 or claim 6, wherein heterocyclic radical represented by R_4 is unsubstituted or substituted by one or more of the same or different substituents selected from halogen atoms and alkyl groups having from 1 to 6 carbon atoms.

8. A compound as claimed in claim 7, wherein R_4 represents an unsubstituted furyl group or a halogen- or alkyl-substituted furyl group.

9. A compound as claimed in claim 8, wherein the furyl group is unsubstituted or mono-substituted by a bromide atom or methyl group.

10. A compound as claimed in claim 1, wherein R_4 represents a methyl, benzhydryl, cyclohexyl, norbornyl, adamantyl or isonicotinyl group.

11. A compound as claimed in any one of claims 1 to 10, wherein

n represents 1 and X represents a hydrogen atom or a hydroxy group, or

n represents 0 and X represents a hydrogen atom.

12. A compound as claimed in claim 11, wherein *n* represents 1 and X represents a hydrogen atom.

13. A compound as claimed in any one of claims 1 to 12, wherein R_1 and R_2, each represents a hydrogen atom or a methoxy group.

14. A compound as claimed in any one of claims 1 to 13, wherein R_3 represents a hydrogen atom or a methyl group.

15. A compound as claimed in claim 12, wherein R_1 and R_2, each represents a hydrogen atom, and R_3 represents a hydrogen atom or a methyl group.

16. A compound as claimed in claim 11, wherein

n represents 0,

X represents a hydrogen atom,

R_1 and R_2 each represents a hydrogen atom, and

R_3 represents a hydrogen atom or a methyl group.

17. A compound as claimed in claim 6, wherein R_3 represents a methyl group.

18. A compound as claimed in claim 6, wherein X represents a hydrogen atom, *n* represents 1, R_1 and R_2, which may be the same or different, each represents a hydrogen atom or a methoxy group; R_3 represents a hydrogen atom or a methyl group; R_4 represents a methyl, benzhydryl, cyclohexyl, norbornyl, adamantyl, isonicotinyl, furyl or mono-substituted furyl group wherein the substituent is a bromine atom or a methyl group, or a phenyl, substituted phenyl, thienyl, pyrrolyl or pyrazinyl group.

19. A compound as claimed in claim 6, wherein R_1 and R_2 each represents a hydrogen atom, R_3 represents a hydrogen atom or methyl group, *n* represents 1, X represents a hydrogen atom and R_4 represents a furyl or a substituted furyl group wherein the substituents are one or more of the same or different substituents selected from bromine atoms and methyl groups.

20. 3-[2-(4-Aminopiperazin-1-yl)ethyl]indole.

21. 3-(4-Aminopiperazin-1-yl)methylindole.

22. 3-[1-Hydroxy-2-(4-aminopiperazin-1-yl)ethyl]indole.

23. 3-[2-(4-Aminopiperazin-1-yl)ethyl]-5,6-dimethoxy-2-methylindole.

24. 3-[2-(4-Benxamidopiperazin-1-yl)ethyl]indole.

25. 3-[1-Hydroxy-2-(4-benzamidopiperazin-1-yl)ethyl]indole.

26. 3-[2-(4-Acetamidopiperazin-1-yl)ethyl]indole.

27. 3-{2-[4-(2-Furoylamido)piperazin-1-yl]ethyl}indole.

28. 3-{2-[4-(5-Bromo-2-furoylamido)piperazin-1-yl]ethyl}indole.

29. 3-{2-[4-(4-Methyl-2-furoylamido)piperazin-1-yl]ethyl}indole.

30. 3-[2-(4-Norbornanecarbonylamidopiperazin-1-yl)ethyl]indole.

31. 3-[2-(4-Benzamidopiperazin-1-yl)ethyl]-2-methylindole.

32. 3-[2-(4-Benzamidopiperazin-1-yl)ethyl]-5,6-dimethoxy-2-methylindole.

33. 3-[2-(4-*p*-Fluorobenzamidopiperazin-1-yl)ethyl]indole.

34. 3-{2-[4-(3,4,5-Trimethoxybenzamido)piperazin-1-yl]ethyl}indole.

35. 3-[2-(4-*p*-Tert-butylbenzamidopiperazin-1-yl)ethyl]indole.

36. 3-[2-(4-*p*-Trifluoromethylbenzamidopiperazin-1-yl)ethyl]indole.

37. 3-[2-(4-*p*-isopropylbenzamidopiperazin-1-yl)ethyl]indole.

38. 3-[2-(4-*p*-Fluorobenzamidopiperazin-1-yl)ethyl]-2-methylindole.

39. 3-[2-(4-*p*-Hydroxybenzamidopiperazin-1-yl)ethyl]indole.

40. 3-{2-[4-(3,5-dimethoxybenzamido)piperazin-1-yl]ethyl}indole.

41. 3-[2-(4-Aminopiperazin-1-yl)ethyl]-5,6-dimethoxy-2-propylindole.

42. 3-[2-(4-Benzamidopiperazin-1-yl)ethyl]-5-ethoxy-2-ethyl-6-methoxyindole.

43. A compound as claimed in claim 1, which is specified in any one of the Examples herein.

44. An acid addition salt of a compound claimed in any one of claims 1 to 16.

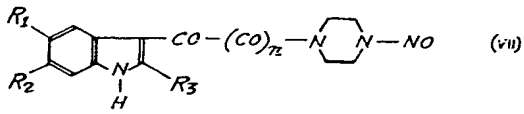
45. A physiologically tolerable acid addition salt of a compound claimed in any one of claims 1 to 16.

46. An acid addition salt of a compound claimed in any one of claims 17 to 43.

47. A physiologically tolerable acid addition salt of a compound claimed in any one of claims 17 to 43.

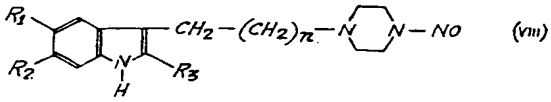
48. A process for the preparation of a compound claimed in claim 1 or an acid addition salt thereof, which comprises

i) reducing a compound of the general formula



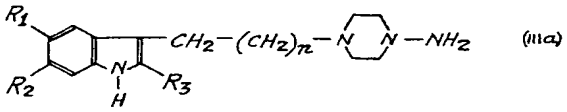
(VII)

or



(VIII)

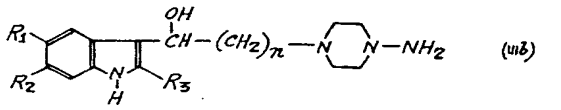
to give a compound of the general formula



(IIIa)

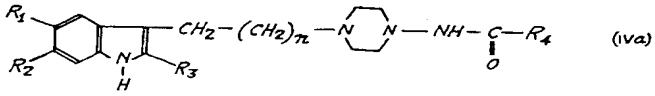
or

ii) partially a compound of the general formula VII above to give a compound of the general formula



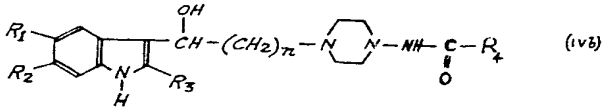
(IIIb)

wherein R_1, R_2, R_3 and n have the meanings given in claim 1, and, if desired, acylating the resulting compound of the general formula IIIa or IIIb to give a compound of the general formula



(IVa)

or



(IVb)

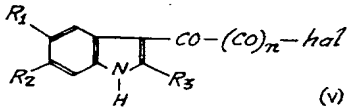
wherein R_1, R_2, R_3, n and R_4 have the meanings given in claim 1.

49. A process as claimed in claim 48, wherein

n represents 1 and X represents a hydrogen atom or a hydroxy group, or

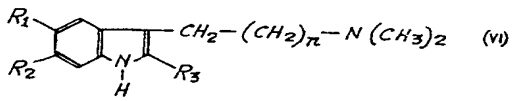
n represents 0 and X represents a hydrogen atom.

50. A process as claimed in claim 49, wherein the starting material of the general formula VII or VIII is prepared by reacting *N*-nitrosopiperazine with a compound of the general formula



(V)

or

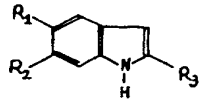


(VI)

wherein hal represents a fluorine, chlorine or bromine atom.

51. A process as claimed in claim 50, wherein in a compound of the formula V n represents 1 and in a compound of the formula VI n represents 0.

52. A process as claimed in claim 51, wherein the compound of the general formula V is prepared by reaction of a compound of the general formula



(IX)

with an oxalyl halide.

53. A process as claimed in claim 52, wherein the compound of the formula V is prepared *in situ* by reacting an acid sensitive indole and a hydrogen halide binder in an immiscible solvent mixture with an oxalyl halide at a temperature in the range of from −10 to 50°C.

54. A process as claimed in claim 53, wherein the hydrogen halide binder is potassium carbonate or triethylamine.

55. A process as claimed in claim 54, wherein the acid sensitive indole is 5,6-dimethoxy-2-indole and the immiscible solvent mixture is a mixture of chloroform and water.

56. A process as claimed in claim 51, wherein the compound of the general formula VIII is 3-(4-nitrosopiperazin-1-yl)methylindole which is prepared by refluxing a mixture of gramine and nitrosopiperazine.

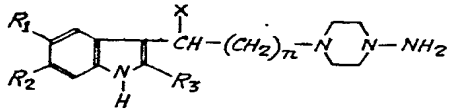
57. A process as claimed in any one of claims 49 to 56, wherein the reduction (i) is carried out with an alkali metal hydride in an inert solvent.

58. A process as claimed in claim 57, wherein the alkali metal hydride is lithium aluminium hydride and the inert solvent is 1,2-dimethoxyethane.

59. A process as claimed in any one of claims 49 to 54, wherein the partial reduction (ii) is carried out with an alkali metal hydride in an inert solvent having a boiling point in the range of from 34 to 66°C.

60. A process as claimed in claim 59, wherein the alkali metal hydride is lithium aluminium hydride and the inert solvent is ether or tetrahydrofuran.

61. A process for the preparation of a compound as claimed in claim 1, wherein Z represents a group of the formula COR_4, or an acid addition salt thereof, which comprises acylating a compound of the general formula



(III)

wherein R_1, R_2, R_3, X and n have the meanings given in claim 1.

62. A process as claimed in any one of claims 48 to 61, wherein the acylation is carried out with an acid, an acyl chloride or an acid anhydride or mixed anhydride.

63. A process as claimed in any one of claims 48 to 62, wherein a resulting 3-[4-(mono-, di- or trimethoxybenzamidopiperazin-1-yl)methyl or ethyl]indole is further demethylated to obtain a mono-, di- or trihydroxybenbamido moiety.

64. A process as claimed in claim 63, wherein a resulting 3-[2-(4-*p*-methoxybenzamidopiperazin-1-yl)ethyl]indole is further demethylated to obtain the hydroxy benzamido moiety.

65. A process as claimed in claim 48, carried out substantially as described herein with reference to methods A, B or C.

66. A process as claimed in claim 61, carried out substantially as described herein.

67. A process as claimed in any one of claims 48 to 61, wherein a compound claimed in any one of claims 17 to 43 or an acid addition salt thereof is produced.

68. A process as claimed in claim 48, carried out substantially as described in any one of the Examples herein.

69. A process as claimed in claim 61, carried out substantially as described in any one of the Examples herein.

70. A compound as claimed in claim 1, wheenever prepared by a process as claimed in any one of claims 48 to 69.

71. An acid addition salt of a compound claimed in claim 1, whenever prepared by a process claimed in any one of claims 48 to 69.

72. A physiologically tolerable acid addition salt of a compound in claim 1, whenever prepared by a process claimed in any one of claims 48 to 69.

73. A pharmaceutical preparation which comprises a compound claimed in any one of claims 1 to 16 and 45 in admixture or conjunction with a pharmaceutically suitable carrier.

74. A pharmaceutical preparation which comprises a compound claimed in any one of claims 17 to 43 and 47 in admixture or conjunction with a pharmaceutically suitable carrier.

75. A pharmaceutical preparation as claimed in claim 73 which is dosage unit form.

76. A pharmaceutical preparation as claimed in claim 74, which is in dosage unit form.

77. A pharmaceutical preparation as claimed in claim 75 which contains from 0.1 to 100 mg of compound of the formula I or salt thereof.

78. A pharmaceutical preparation as claimed in claim 76, which contains from 0.1 to 100 mg of compound of the formula I or salt thereof.

ABEL & IMRAY,
Chartered Patent Agents,
Northumberland House,
303—306 High Holborn,
London WC1V 7LH.

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